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Novel Phenoxyalkylamine Derivatives. V.[1] Synthesis, α-Blocking Activity and Quantitative Structure–Activity Analysis of α-[(Phenoxyethylamino)propyl]-α-phenylacetonitrile Derivatives

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α-[(Phenoxyethylamino)propyl]-α-phenylacetonitrile derivatives possessing various substituents on the benzene ring (A ring) at the phenylacetonitrile moiety, on the quaternary carbon atom and on the benzene ring (B ring) at the phenoxy moiety, and exhibiting various degrees of α-blocking activity, were prepared. The variations in the activity were analyzed qualitatively as well as quantitatively by using physicochemical substituent parameters and a regression technique. The effect of substituents on the A ring was rationalized in terms of a parabolic function of their hydrophobic parameter. As regards substituents on the quaternary carbon atom, alkyl groups were desirable for high activity. The effects of substituents on the B ring were such that an optimum hydrophobic condition exists and that an alkoxy substituent at the *o*-position as well as smaller substituents at the *m*- and *p*-positions are favorable for high activity. The analysis for the combined series of analogs where substituents on the A and B rings are varied showed the existence of an optimum hydrophobicity for the whole molecule for the transport process of the molecule, besides above-mentioned various position-specific structural effects.

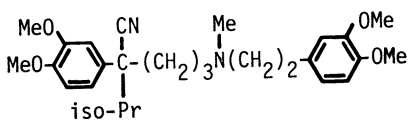
Keywords——phenoxyalkylamine; α-[(phenoxyethylamino)propyl]-α-phenylacetonitrile; α-blocking activity; quantitative structure–activity relationship; Hansch–Fujita analysis

As a part of our studies of cardiovascular agents, we designed and synthesized novel phenoxyalkylamine derivatives (I) which are considered as analogs of verapamil.[2] We examined them for two types of pharmacological activities, namely, Ca^{2+}-antagonistic and α-blocking activities. The effects of the carbon chain length, *m* and *n*, of the alkylene parts and the substituent at the amino nitrogen on these activities were examined and it was shown that structural conditions of $m=n=3$ and $R_1=Me$ were desirable for Ca^{2+}-antagonistic activity, while those of $m=3$, $n=2$ and $R_1=H$ (I′) were favorable for α-blocking activity.[3]

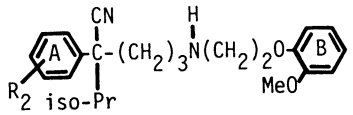
The aim of the present study was to investigate the effect of structural modifications of I on the α-blocking activity, under conditions of $m=3$, $n=2$ and $R_1=H$. We attempted to examine compounds in which various substituents, R_2, were introduced into the A ring (II-1—22), alkyl and alkoxyalkyl substituents, R_3, were placed on the quaternary carbon atom (II-23—30) and various substituents, R_4, were attached to the B ring (II-31—68). We report here the synthesis of these compounds and the relationships of their structure with the α-blocking activity.

Synthesis

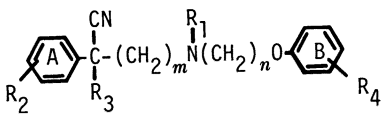
α-[(Phenoxyethylamino)propyl]-α-phenylacetonitrile derivatives (II) were synthesized by the method shown in Chart 2.



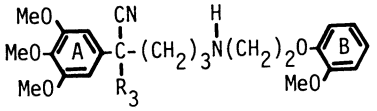
verapamil



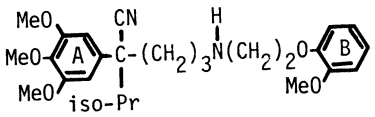
II-1-22



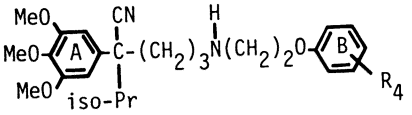
I



II-23-30



I′



II-31-68

Chart 1

The desired compounds (II) were obtained by the reductive condensation of α-(2-formylethyl)-α-phenylacetonitriles (III) with phenoxyethylamines using sodium borohydride (method A) or by the reaction of α-(3-chloropropyl)-α-isopropyl-α-phenylacetonitriles (IV) with phenoxyethylamines (method B). The NO_2 derivatives (II-18, 38, 50, 60) were hydrogenated to give the corresponding NH_2 analogs (II-19, 39, 51, 61). The $R_4 = o\text{-}OCH_2Ph$ derivative (II-43) was debenzylated reductively to yield the $R_4 = o\text{-}OH$ derivative (II-44). The preparation of all starting materials (III, IV) was described previously.[3-5]

The physicochemical properties of II are summarized in Tables I—III.

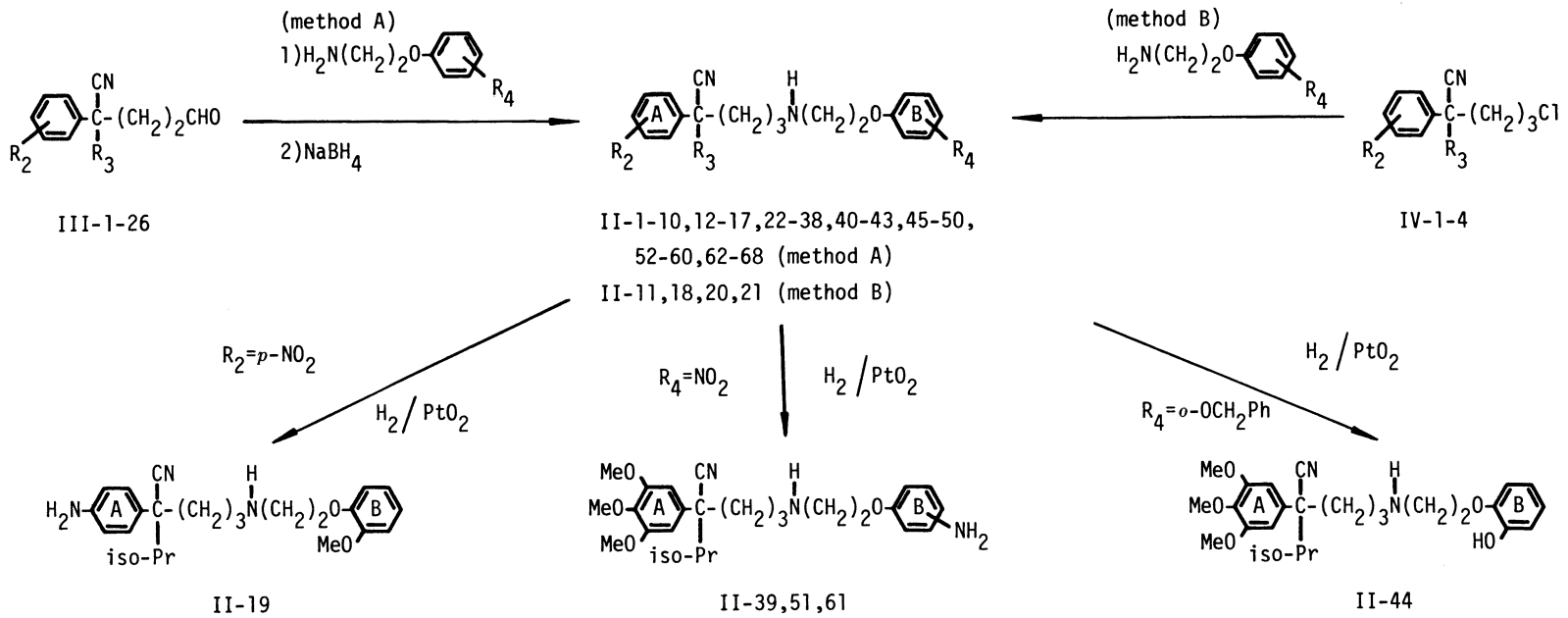
Results and Discussion

The α-blocking activity is shown as the pA_2 value in Tables I—III.

The Effect of Substituent R_2 (Table I)

First, we examined the effect of the substituent R_2 on the A ring while the substituents R_3 and R_4 were fixed as iso-Pr and *o*-OMe, respectively. Among compounds (II-1—21) monosubstituted at the *o*-, *m*- or *p*-position on the A ring, the *p*-OMe (II-14) and *p*-NO_2 (II-18) derivatives showed activities close to $pA_2 = 8$. The 3,4-$(OMe)_2$ derivative (II-22) with the *p*-OMe group exhibited an activity higher than $pA_2 = 8$, but its activity was lower than that of the 3,4,5-$(OMe)_3$ derivative (I′) reported previously.[3]

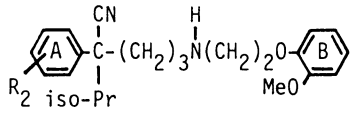
To understand the physicochemical background of the effect of substituent R_2 on the α-blocking activity, we have performed quantitative structure–activity analyses using physicochemical substituent parameters and a regression technique.[7] We analyzed the pA_2 value of unsubstituted (II-1) and monosubstituted derivatives (II-2—21) using single parameters. The result indicated that the activity was correlated best with a parabolic function of the hydrophobic parameter π as shown in Eq. 2 in Table IV with a satisfied quality of the correlation. The π value used here is that for monosubstituted benzenes.[8] In Fig. 1, the



III-1: R_2=H,R_3=iso-Pr
III-2: R_2=*o*-Me,R_3=iso-Pr
III-3: R_2=*o*-OMe,R_3=iso-Pr
III-4: R_2=*o*-F,R_3=iso-Pr
III-5: R_2=*o*-Cl,R_3=iso-Pr
III-6: R_2=*o*-Br,R_3=iso-Pr
III-7: R_2=*m*-Me,R_3=iso-Pr
III-8: R_2=*m*-OMe,R_3=iso-Pr
III-9: R_2=*m*-F,R_3=iso-Pr
III-10: R_2=*m*-Cl,R_3=iso-Pr
III-11: R_2=*p*-Me,R_3=iso-Pr
III-12: R_2=*p*-iso-Pr,R_3=iso-Pr
III-13: R_2=*p*-OMe,R_3=iso-Pr
III-14: R_2=*p*-F,R_3=iso-Pr
III-15: R_2=*p*-Cl,R_3=iso-Pr
III-16: R_2=*p*-Br,R_3=iso-Pr
III-17: R_2=3,4-$(OMe)_2$,R_3=iso-Pr
III-18: R_2=3,4,5-$(OMe)_3$,R_3=H
III-19: R_2=3,4,5-$(OMe)_3$,R_3=Me
III-20: R_2=3,4,5-$(OMe)_3$,R_3=Et
III-21: R_2=3,4,5-$(OMe)_3$,R_3=*n*-Pr
III-22: R_2=3,4,5-$(OMe)_3$,R_3=*n*-Bu
III-23: R_2=3,4,5-$(OMe)_3$,R_3=iso-Bu
III-24: R_2=3,4,5-$(OMe)_3$,R_3=$(CH_2)_2OMe$
III-25: R_2=3,4,5-$(OMe)_3$,R_3=$(CH_2)_2OEt$
III-26: R_2=3,4,5-$(OMe)_3$,R_3=iso-Pr
IV-1: R_2=*m*-$CONMe_2$
IV-2: R_2=*p*-NO_2
IV-3: R_2=NHAc
IV-4: R_2=*p*-$CONMe_2$

Chart 2

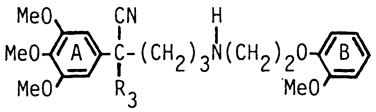
TABLE I. Physicochemical and Pharmacological Data for R_2-Substituted α-Isopropyl-α-[(phenoxyethylamino)propyl]-α-phenylacetonitriles (II-1—22)



Compd. No.	R_2	Yield[a] (%) (Method)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C H N	pA_2
II-1	H	87 (A)	Free	Oil	—	$C_{23}H_{30}N_2O_2$	366.2307[c] (366.2318)	7.75
II-2	*o*-Me	70 (A)	f	141.5—143	EtOH–Et_2O	$C_{24}H_{32}N_2O_2 \cdot C_4H_4O_4$	67.72 7.31 5.64 (67.45 7.49 5.53)	7.54
II-3	*o*-OMe	54 (A)	o	139—140	EtOH–iso-Pr_2O	$C_{24}H_{32}N_2O_3 \cdot C_2H_2O_4$	64.18 7.04 5.76 (63.93 7.40 5.61)	7.65
II-4	*o*-F	63 (A)	HCl	89—90	EtOH–Et_2O	$C_{23}H_{29}FN_2O_2 \cdot HCl \cdot 1/2\,H_2O$	64.25 7.27 6.52 (64.64 7.51 6.48)	7.42
II-5	*o*-Cl	58 (A)	HCl	96—97	EtOH–Et_2O	$C_{23}H_{29}ClN_2O_2 \cdot HCl \cdot H_2O$	60.66 7.08 6.15 (60.79 7.36 5.90)	7.11
II-6	*o*-Br	51 (A)	f	141—143	EtOH–Et_2O	$C_{23}H_{29}BrN_2O_2 \cdot C_4H_4O_4$	57.76 5.92 4.99 (57.48 5.98 4.89)	7.24
II-7	*m*-Me	48 (A)	f	126—127.5	EtOH–Et_2O	$C_{24}H_{32}N_2O_2 \cdot C_4H_4O_4$	67.72 7.31 5.64 (67.78 7.35 5.54)	7.47
II-8	*m*-OMe	86 (A)	HCl	128—129	EtOH–Et_2O	$C_{24}H_{32}N_2O_3 \cdot HCl$	66.58 7.68 6.47 (66.49 7.64 6.24)	7.87
II-9	*m*-F	68 (A)	f	157.5—159.5	EtOH	$C_{23}H_{29}FN_2O_2 \cdot C_4H_4O_4$	64.79 6.64 5.60 (64.70 6.49 5.42)	7.90
II-10	*m*-Cl	70 (A)	f	153—154.5	EtOH–Et_2O	$C_{23}H_{29}ClN_2O_2 \cdot C_4H_4O_4$	62.72 6.43 5.42 (62.37 6.50 5:09)	7.66
II-11	*m*-$CONMe_2$	51 (B)	Free	Oil	—	$C_{26}H_{35}N_3O_3$	437.2678[c] (437.2690)	7.60
II-12	*p*-Me	34 (A)	m	127.5—130	EtOH	$C_{24}H_{32}N_2O_2 \cdot C_4H_4O_4$	67.72 7.31 5.64 (67.65 7.28 5.57)	7.32
II-13	*p*-iso-Pr	30 (A)	HCl	153—154.5	EtOH–Et_2O	$C_{26}H_{36}N_2O_2 \cdot HCl$	70.17 8.38 6.29 (69.95 8.06 6.06)	6.87
II-14	*p*-OMe	72 (A)	Free	Oil	—	$C_{24}H_{32}N_2O_3$	396.2413[c] (396.2410)	8.02
II-15	*p*-F	72 (A)	m	148—149	EtOH	$C_{23}H_{29}FN_2O_2 \cdot C_4H_4O_4$	64.79 6.64 5.60 (64.51 6.88 5.49)	7.57
II-16	*p*-Cl	57 (A)	m	161.5—163.5	EtOH	$C_{23}H_{29}ClN_2O_2 \cdot C_4H_4O_4$	62.72 6.43 5.42 (62.61 6.25 5.08)	7.35
II-17	*p*-Br	60 (A)	f	85—90	EtOH–Et_2O	$C_{23}H_{29}BrN_2O_2 \cdot 1/2\,C_4H_4O_4 \cdot H_2O$	57.58 6.38 5.37 (57.31 6.47 5.04)	7.28
II-18	*p*-NO_2	73 (B)	m	184—186	MeOH	$C_{23}H_{29}N_3O_4 \cdot C_4H_4O_4$	61.47 6.30 7.96 (61.43 6.30 7.81)	8.04
II-19	*p*-NH_2	93	o	155—158	H_2O–EtOH	$C_{23}H_{31}N_3O_2 \cdot 2C_2H_2O_4$	57.75 6.28 7.48 (57.68 6.35 7.41)	7.85
II-20	*p*-NHAc	74 (B)	Free	Oil	—	$C_{25}H_{33}N_3O_3$	423.2522[c] (423.2518)	7.68
II-21	*p*-$CONMe_2$	65 (B)	Free	Oil	—	$C_{26}H_{35}N_3O_3$	437.2678[c] (437.2685)	7.88
II-22	3,4-$(OMe)_2$	88 (A)	m	130—132	EtOH–iso-Pr_2O	$C_{25}H_{34}N_2O_4 \cdot C_4H_4O_4$	64.19 7.06 5.16 (63.80 7.19 5.12)	8.25
I'[d]	3,4,5-$(OMe)_3$							8.42

a) Yield of the free base. *b*) f, fumarate; o, oxalate; m, maleate. *c*) MW determined by high-resolution mass spectrography. *d*) Ref. 3.

TABLE II. Physicochemical and Pharmacological Data for R_3-Substituted α-[(Phenoxyethylamino)propyl]-α-phenylacetonitriles (II-23—30)



Compd. No.	R_3	Yield[a] (%) (Method)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2
II-23	H	60 (A)	HCl	112—114	EtOH–Et_2O	$C_{23}H_{30}N_2O_5 \cdot HCl \cdot H_2O$	58.91 (58.50	7.09 7.16	5.97 5.87)	7.83
II-24	Me	70 (A)	f	118—119	EtOH	$C_{24}H_{32}N_2O_5 \cdot C_4H_4O_4$	61.75 (61.54	6.66 6.83	5.14 5.06)	8.40
II-25	Et	74 (A)	f	143.5—144	EtOH	$C_{25}H_{34}N_2O_5 \cdot C_4H_4O_4$	62.35 (62.17	6.86 6.92	5.01 4.83)	8.79
II-26	*n*-Pr	60 (A)	f	151—152	EtOH	$C_{26}H_{36}N_2O_5 \cdot C_4H_4O_4$	62.92 (62.63	7.04 7.38	4.89 4.75)	8.46
II-27	*n*-Bu	46 (A)	Free	Oil	—	$C_{27}H_{38}N_2O_5$	.470.2781[c] (470.2787)			8.57
II-28	iso-Bu	87 (A)	f	150—153	EtOH	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4$	63.47 (63.42	7.22 7.26	4.77 4.68)	8.67
II-29	$(CH_2)_2OMe$	41. (A)	o	175—176	MeOH–Et_2O	$C_{26}H_{36}N_2O_6 \cdot C_2H_2O_4$	59.78 (59.65	6.81 6.97	4.98 4.89)	7.76
II-30	$(CH_2)_2OEt$	41 (A)	o	160—161	MeOH	$C_{27}H_{38}N_2O_6 \cdot C_2H_2O_4$	60.40 (60.17	6.99 7.14	4.86 4.82)	7.46
I'[d]	iso-Pr									8.42

a) Yield of the free base. *b*) f, fumarate; o, oxalate. *c*) MW determined by high-resolution mass spectrography. *d*) Ref. 3.

situation of the correlation is illustrated. The π values used in this analysis are listed in Table V.

In Eq. 2, the 3,4-$(OMe)_2$ (II-22) and 3,4,5-$(OMe)_3$ (I') derivatives were not included. The activity of these compounds was higher than expected from the parabola, as shown in Fig. 1. The higher activity of the 3,4-$(OMe)_2$ and 3,4,5-$(OMe)_3$ derivatives is consistent with the fact that the activity of *m*-OMe and *p*-OMe analogs also deviated upward to some extent, although the reason for this is not clear.

Equation 2 shows that π values between −0.3 and −0.4 are favorable for the activity. The fact that the *p*-NO_2 derivative (II-18) was the most effective among the monosubstituted compounds could be rationalized in terms of Eq. 2.

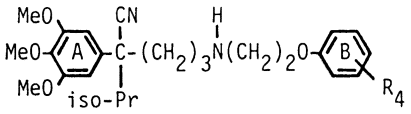
The Effect of Substituent R_3 (Table II)

Compounds where the substituent R_3 is alkyl (II-24—28) exhibited a potency higher than $pA_2 = 8$. The unsubstituted (II-23) and alkoxyalkyl (II-29, 30) analogs showed lower activity. Since the activity is highest in the Et derivative, an optimum hydrophobicity seems to exist also for R_3. Unfortunately, quantitative analyses of the effect of R_3 gave no significant correlation, since the number of compounds in the set used is too small.

The Effect of Substituent R_4 (Table III)

Among derivatives monosubstituted on the B ring, *o*-substituted derivatives such as the *o*-OMe (I') and *o*-OEt (II-35) analogs exhibited higher potency. Bulkier alkoxy groups decreased the activity. Since the *o*-OMe group was thought to be favorable for potent activity among various substituents, disubstituted analogs with the *o*-OMe group were synthesized.

TABLE III. Physicochemical and Pharmacological Data for R_4-Substituted α-Isopropyl-α-[(phenoxyethyl-amino)propyl]-α-phenylacetonitriles (II-31—68)



Compd. No.	R_4	Yield[a] (%) (Method)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2
II-31	H	61 (A)	HCl	175—176	EtOH–iso-Pr_2O	$C_{25}H_{34}N_2O_4 \cdot HCl$	64.85 (64.47	7.62 7.67	6.05 5.86)	7.37
II-32	*o*-Me	39 (A)	HCl	165—168	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_4 \cdot HCl$	65.47 (65.07	7.82 8.15	5.87 5.88)	6.57
II-33	*o*-*n*-Pr	65 (A)	f	157—158	EtOH–iso-Pr_2O	$C_{28}H_{40}N_2O_4 \cdot C_4H_4O_4$	65.73 (65.68	7.58 7.58	4.79 4.65)	6.30
II-34	*o*-*tert*-Bu	60 (A)	f	146—148	MeOH–iso-Pr_2O	$C_{29}H_{42}N_2O_4 \cdot C_4H_4O_4$	66.20 (65.99	7.74 7.77	4.68 4.53)	5.57
II-35	*o*-OEt	60 (A)	HCl	167.5—170	EtOH	$C_{27}H_{38}N_2O_5 \cdot HCl$	63.96 (63.62	7.75 7.78	5.52 5.10)	8.48
II-36	*o*-F	53 (A)	f	139—141	EtOH–iso-Pr_2O	$C_{25}H_{33}FN_2O_4 \cdot C_4H_4O_4$	62.13 (61.82	6.65 6.99	5.00 4.73)	7.45
II-37	*o*-Cl	69 (A)	f	147—148	EtOH	$C_{25}H_{33}ClN_2O_4 \cdot C_4H_4O_4$	60.36 (60.38	6.46 6.67	4.85 4.64)	6.91
II-38	*o*-NO_2	51 (A)	f	171—172	EtOH–iso-Pr_2O	$C_{25}H_{33}N_3O_6 \cdot C_4H_4O_4$	59.28 (59.07	6.35 6.48	7.15 6.95)	7.01
II-39	*o*-NH_2	97	Free	Oil	—	$C_{25}H_{35}N_3O_4$	441.2628[c] (441.2617)			6.53
II-40	*o*-CN	36 (A)	f	165—166	EtOH	$C_{26}H_{33}N_3O_4 \cdot C_4H_4O_4$	63.48 (63.27	6.57 6.96	7.40 7.32)	7.44
II-41	*o*-OPr	76 (A)	f	162.5—164	EtOH–Et_2O	$C_{28}H_{40}N_2O_5 \cdot C_4H_4O_4$	63.98 (63.99	7.38 7.69	4.66 4.56)	7.57
II-42	*o*-OBu	65 (A)	o	128.5—130	EtOH–iso-Pr_2O	$C_{29}H_{42}N_2O_5 \cdot 1/2\,C_2H_2O_4 \cdot 1/2\,H_2O$	65.20 (64.94	8.02 7.90	5.07 4.88)	7.37
II-43	*o*-OCH_2Ph	52 (A)	o	164—165	MeOH	$C_{32}H_{40}N_2O_5 \cdot 1/2\,C_2H_2O_4 \cdot 1/2\,H_2O$	67.56 (67.76	7.22 7.34	4.77 4.78)	6.90
II-44	*o*-OH	60	f	190.5—192.5	MeOH	$C_{25}H_{34}N_2O_5 \cdot C_4H_4O_4$	62.35 (62.18	6.86 6.70	5.01 4.95)	7.55
II-45	*m*-Me	46 (A)	HCl	153—156	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_4 \cdot HCl \cdot 1/2\,H_2O$	64.25 (64.34	7.88 7.74	5.76 5.57)	6.30
II-46	*m*-*tert*-Bu	92 (A)	f	159—160	EtOH–iso-Pr_2O	$C_{29}H_{42}N_2O_4 \cdot C_4H_4O_4$	66.20 (65.96	7.74 8.03	4.68 4.52)	5.37
II-47	*m*-OMe	33 (A)	HCl	103—105	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_5 \cdot HCl$	63.34 (62.98	7.56 7.85	5.68 5.71)	6.34
II-48	*m*-F	77 (A)	f	180—181	EtOH	$C_{25}H_{33}FN_2O_4 \cdot C_4H_4O_4$	62.13 (62.32	6.65 6.90	5.00 4.99)	7.35
II-49	*m*-Cl	50 (A)	f	163—165	MeOH–Et_2O	$C_{25}H_{33}ClN_2O_4 \cdot C_4H_4O_4$	60.36 (60.73	6.46 6.52	4.85 4.51)	6.63
II-50	*m*-NO_2	87 (A)	f	162—163	EtOH–iso-Pr_2O	$C_{25}H_{33}N_3O_6 \cdot C_4H_4O_4$	59.28 (59.03	6.35 6.52	7.15 7.12)	6.30
II-51	*m*-NH_2	98	f	162—164	EtOH–iso-Pr_2O	$C_{25}H_{35}N_3O_4 \cdot 1/2\,C_4H_4O_4 \cdot 3/2\,H_2O$	61.58 (61.69	7.66 7.31	7.98 7.72)	5.94
II-52	*m*-CN	52 (A)	o	162—163	EtOH	$C_{26}H_{33}N_3O_4 \cdot C_2H_2O_4 \cdot H_2O$	60.10 (60.48	6.66 7.04	7.51 7.18)	6.11
II-53	*m*-CF_3	81 (A)	f	110—111	EtOH–iso-Pr_2O	$C_{26}H_{33}F_3N_2O_4 \cdot C_4H_4O_4 \cdot H_2O$	57.32 (57.48	6.25 6.14	4.46 4.20)	5.48

TABLE III.(continued)

Compd. No.	R_4	Yield[a] (%) (Method)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2
II-54	*p*-Me	73 (A)	f	167—168	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_4 \cdot C_4H_4O_4$	64.73 (64.64)	7.24 (7.25)	5.03 (4.82)	6.31
II-55	*p*-*n*-Pr	63 (A)	f	145—147	EtOH–iso-Pr_2O	$C_{28}H_{40}N_2O_4 \cdot C_4H_4O_4$	65.73 (65.59)	7.58 (7.80)	4.79 (4.56)	5.23
II-56	*p*-*tert*-Bu	69 (A)	f	151—152	MeOH–iso-Pr_2O	$C_{29}H_{42}N_2O_4 \cdot C_4H_4O_4$	66.20 (65.99)	7.74 (8.05)	4.68 (4.53)	5.24
II-57	*p*-OMe	67 (A)	f	160.5—162	EtOH–iso-Pr_2O	$C_{26}H_{36}N_2O_5 \cdot C_4H_4O_4$	62.92 (63.01)	7.04 (6.98)	4.89 (4.68)	5.86
II-58	*p*-F	56 (A)	Free	Oil	—	$C_{25}H_{33}FN_2O_4$	444.2424[c] (444.2437)			6.36
II-59	*p*-Cl	70 (A)	Free	Oil	—	$C_{25}H_{33}ClN_2O_4$	460.2129[c] (460.2151) 462.2099[c] (462.2100)			5.84
II-60	*p*-NO_2	64 (A)	f	191—193	MeOH	$C_{25}H_{33}N_3O_6 \cdot C_4H_4O_4$	59.28 (59.17)	6.35 (6.35)	7.15 (7.11)	5.42
II-61	*p*-NH_2	59	f	152—154	EtOH–iso-Pr_2O	$C_{25}H_{35}N_3O_4$ $C_4H_4O_4 \cdot 1/4H_2O$	61.96 (61.86)	7.08 (7.12)	7.47 (7.35)	6.26
II-62	*p*-CN	65 (A)	o	190.5—192.5	MeOH–EtOH	$C_{26}H_{33}N_3O_4 \cdot C_2H_2O_4$	62.10 (61.93)	6.51 (6.67)	7.76 (7.67)	5.64
II-63	2,3-$(OMe)_2$	79 (A)	HCl	151—153	EtOH–Et_2O	$C_{27}H_{38}N_2O_6 \cdot HCl$	62.00 (61.79)	7.52 (7.60)	5.36 (5.29)	5.71
II-64	2,4-$(OMe)_2$	76 (A)	f	133—134	EtOH–Et_2O	$C_{27}H_{38}N_2O_6 \cdot C_4H_4O_4$	61.78 (61.39)	7.02 (7.08)	4.65 (4.43)	6.04
II-65	2,5-$(OMe)_2$	77 (A)	f	142—145	EtOH	$C_{27}H_{38}N_2O_6 \cdot C_4H_4O_4$	61.78 (61.75)	7.02 (7.14)	4.65 (4.60)	6.81
II-66	2,6-$(OMe)_2$	64 (A)	HCl	186—189	EtOH	$C_{27}H_{38}N_2O_6 \cdot HCl$	62.00 (61.91)	7.52 (7.66)	5.36 (5.20)	6.09
II-67	2-OMe,5-Me	98 (A)	Free	Oil	—	$C_{27}H_{38}N_2O_5$	470.2781[c] (470.2776)			7.34
II-68	2-OMe,5-F	86 (A)	f	141—142	iso-PrOH	$C_{26}H_{35}FN_2O_5$ $\cdot C_4H_4O_4$	61.01 (60.88)	6.66 (6.71)	4.74 (4.69)	8.69
I′[d]	*o*-OMe									8.42
Prazosin[e]										8.63

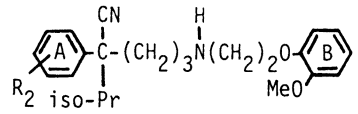
a) Yield of the free base. *b*) f, fumarate; o, oxalate. *c*) MW determined by high-resolution mass spectrography. *d*) Ref. 3. *e*) Reference α-blocker.[6]

TABLE IV. Development of the Correlation Equations for the α-Blocking Activity of R_2-Substituted Derivatives (II-1—21)

Eq. No.	π	π^2	Const.	n[a]	r[b]	s[c]	$F_{l,n-m-1}$[d]
1	−0.30 (0.14)[e]		7.62 (0.10)	21	0.71	0.22	18.96
2	−0.23 (0.14)	−0.30 (0.11)	7.73 (0.11)	21	0.84	0.18	12.00

a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed F value: l, the number of additional parameter terms; m, the number of total parameter terms. Theoretical F values are $F_{1,19;\alpha=0.05}=4.38$ for Eq. 1 and $F_{1,18;\alpha=0.05}=4.41$ for Eq. 2. *e*) Figures in parentheses are 95% confidence intervals.

TABLE V. α-Blocking Activity and Physicochemical Parameters of R_2-Substituted Derivatives (II-1—22, I′)



Compd. No.	R_2	π[a]	pA_2	
			Obsd.	Eq. 2 Calcd. (Δ)[b]
II-1	H	0.00	7.75	7.73 (0.02)
II-2	*o*-Me	0.56	7.54	7.50 (0.04)
II-3	*o*-OMe	−0.02	7.65	7.74 (−0.09)
II-4	*o*-F	0.14	7.42	7.69 (−0.27)
II-5	*o*-Cl	0.71	7.11	7.41 (−0.30)
II-6	*o*-Br	0.86	7.24	7.31 (−0.07)
II-7	*m*-Me	0.56	7.47	7.50 (−0.03)
II-8	*m*-OMe	−0.02	7.87	7.74 (0.13)
II-9	*m*-F	0.14	7.90	7.69 (0.21)
II-10	*m*-Cl	0.71	7.66	7.41 (0.25)
II-11	*m*-$CONMe_2$	−1.05[c]	7.60	7.80 (−0.20)
II-12	*p*-Me	0.56	7.32	7.50 (−0.18)
II-13	*p*-iso-Pr	1.53	6.87	6.75 (0.12)
II-14	*p*-OMe	−0.02	8.02	7.74 (0.28)
II-15	*p*-F	0.14	7.57	7.69 (−0.12)
II-16	*p*-Cl	0.71	7.35	7.41 (−0.06)
II-17	*p*-Br	0.86	7.28	7.31 (−0.03)
II-18	*p*-NO_2	−0.28	8.04	7.80 (0.24)
II-19	*p*-NH_2	−1.23	7.85	7.76 (0.09)
II-20	*p*-NHAc	−0.97	7.68	7.81 (−0.13)
II-21	*p*-$CONMe_2$	−1.05[c]	7.88	7.80 (0.08)
II-22[d]	3,4-$(OMe)_2$	−0.04[e]	8.25	7.74
I′[d]	3,4,5-$(OMe)_3$	−0.06[e]	8.42	7.74

a) π value for monosubstituted benzene series. *b*) Δ, the difference between observed and calculated values. *c*) Estimated from the equation $\pi(CONMe_2)=\pi(CONHMe)+[\pi(CONHMe)-\pi(CONH_2)]$. *d*) Omitted from the calculation. *e*) Values are the sum of the values for the substituents at each position.

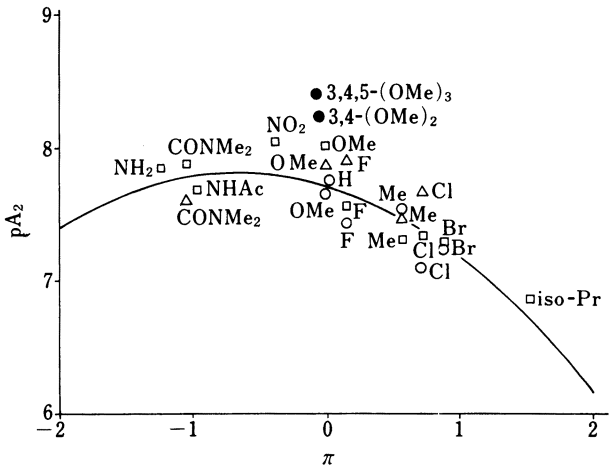


Fig. 1. Plots of pA_2 *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative; ●, disubstituted derivative.

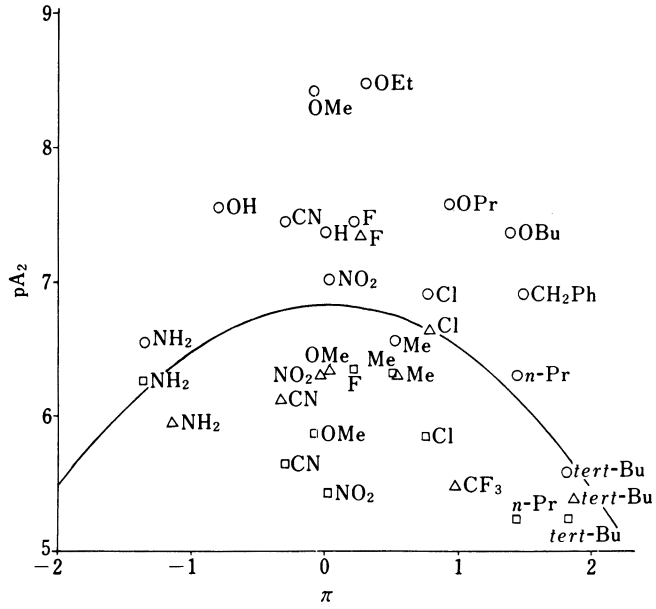


Fig. 2. Plots of pA_2 *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

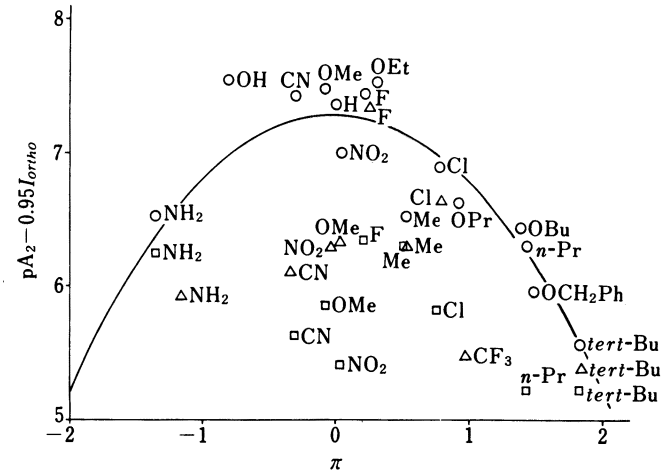


Fig. 3. Plots of $pA_2 - 0.95I_{ortho}$ *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

Contrary to our expectation, the activities of all dimethoxy derivatives including the 2,6-$(OMe)_2$ analog (II-66), which possesses two *o*-OMe groups, were low, but the 2-OMe-5-F derivative (II-68) exhibited an activity higher than that of the *o*-OMe derivative itself (I′). The activity of II-68 was close to that of prazosin, a typical α-blocker.[6]

The quantitative analysis for unsubstituted (II-31) and monosubstituted derivatives (II-32—62, I′) using single parameters showed that the activity was correlated best by a quadratic equation of the hydrophobic parameter π, as shown by Eq. 3 in Table VI, although the quality of correlation was not satisfactory. The π value used here is that for substituted

TABLE VI. Development of the Correlation Equations for the α-Blocking Activity of R_4-Substituted Derivatives (II-31—65, 67, 68, I′)

Eq. No.	π^2	I_{ortho}	ΔL_{para}	ΔB_5^{meta}	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}{}^{d)}$
3	−0.35				6.83	33	0.43	0.80	6.92
	(0.27)[e)]				(0.37)				
4	−0.37	1.50			6.63	33	0.76	0.59	27.35
	(0.20)	(0.58)			(0.28)				
5	−0.33	1.28	−0.43		6.81	33	0.85	0.49	15.16
	(0.16)	(0.50)	(0.23)		(0.25)				
6	−0.30	1.02	−0.57	−0.47	7.03	33	0.90	0.40	14.59
	(0.14)	(0.43)	(0.20)	(0.25)	(0.24)				
7	−0.28	0.95	−0.66	−0.54	7.08	38	0.90	0.43	34.01
	(0.14)	(0.34)	(0.19)	(0.21)	(0.25)				

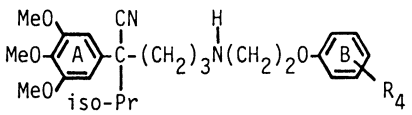
a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed *F* value: *l*, the number of additional parameter terms; *m*, the number of total parameter terms. Theoretical *F* values are $F_{1,31:\alpha=0.05}=4.16$ for Eq. 3, $F_{1,30:\alpha=0.05}=4.17$ for Eq. 4, $F_{1,29:\alpha=0.05}=4.18$ for Eq. 5, $F_{1,28:\alpha=0.05}=4.20$ for Eq. 6 and $F_{4,33:\alpha=0.05}=2.66$ for Eq. 7. *e*) Figures in parentheses are 95% confidence intervals.

anisoles estimated according to the equation given in the experimental section. In Fig. 2, the correlation is illustrated. In trying to improve the correlation, we noticed that the activity of *o*-alkoxy derivatives deviated markedly upward from the parabola. By introducing an indicator variable I_{ortho} which takes the value of one for *o*-alkoxy derivatives, Fig. 3 was drawn. The coefficient, −0.95, of the I_{ortho} term added to pA_2 on the ordinate was selected so that at least the plot for the *ortho* derivatives was aligned as well as possible, as shown by the solid line. We further noticed in Fig. 3 that most of the *m*- and *p*-substituted derivatives deviated downward from the parabola regardless of the electronic properties of the substituent, the deviations for the *p*-substituted derivatives being mostly larger. These facts suggest that position-specific steric effects may participate at the *m*- and *p*-positions.

By considering the position-specific steric parameters, ΔB_5 for the *m*-substituents and ΔL for the *p*-substituents, in addition to π^2 and the indicator variable I_{ortho}, Eq. 6 was derived, where the linear term of π is insignificant; L[9] represents the length of substituents along an axis connecting the α-atom of the substituent and the rest of the molecule, and B_5[10] is the maximum width of the substituent from the L axis. For the sake of simplicity, the values relative to that of H were used: $\Delta L = L(X) - L(H)$ and $\Delta B_5 = B_5(X) - B_5(H)$. The stepwise development of Eq. 6 justified statistically for thirty-three derivatives is shown in Table VI. The physicochemical parameters of each substituent used in this analysis are listed in Table VII.

The I_{ortho} parameter probably accounts for a stereospecific hydrogen-bond accepting effect of the *o*-alkoxy groups. This type of hydrogen-bonding effect was shown to be expressible by an indicator variable.[11] The hydrogen-bond formation may be either with an acidic group on the receptor or with the NH hydrogen in the *o*-alkoxy derivatives. In Eq. 7 and Fig. 4, five disubstituted compounds where one of the substituents is *o*-OMe were included, but not the 2,6-$(OMe)_2$ derivative (II-66). The I_{ortho} was not assigned to the *o*-alkoxy substituent, which may not work as a hydrogen-bond acceptor. Thus, $I_{ortho}=1$ was applied to the 2,4-$(OMe)_2$ (II-64), 2,5-$(OMe)_2$ (II-65), 2-OMe-5-Me (II-67) and 2-OMe-5-F (II-68) derivatives, but not to the 2,3-$(OMe)_2$ analog (II-63). Being sandwiched by the oxyalkylene bridge and the 3-OMe, the *o*-OMe group in II-63 could not take such a conformation for intra- or intermolecular hydrogen-bond formation as that in II-64—68. The activity of the 2,6-$(OMe)_2$ compound (II-66) was much lower than that expected for $I_{ortho}=0$. The reason is not clear, but a buttressing effect of vicinally located 6-OMe and oxyalkylene groups may be

TABLE VII. α-Blocking Activity and Physicochemical Parameters of R_4-Substituted Derivatives (II-31—68, I′)



No.	R_4	π[a]	I_{ortho}[b]	ΔL_{para}[c]	ΔB_5^{meta}[c]	pA_2 Obsd.	pA_2 Eq. 7 Calcd. (Δ)[d]
II-31	H	0.00	0.00	0.00	0.00	7.37	7.08 (0.29)
II-32	*o*-Me	0.52	0.00	0.00	0.00	6.57	7.01 (−0.44)
II-33	*o*-*n*-Pr	1.43	0.00	0.00	0.00	6.30	6.51 (−0.21)
II-34	*o*-*tert*-Bu	1.82	0.00	0.00	0.00	5.57	6.15 (−0.58)
I′	*o*-OMe	−0.08	1.00	0.00	0.00	8.42	8.03 (0.39)
II-35	*o*-OEt	0.30	1.00	0.00	0.00	8.48	8.00 (0.48)
II-36	*o*-F	0.21	0.00	0.00	0.00	7.45	7.07 (0.38)
II-37	*o*-Cl	0.77	0.00	0.00	0.00	6.91	6.92 (−0.01)
II-38	*o*-NO_2	0.03	0.00	0.00	0.00	7.01	7.08 (−0.07)
II-39	*o*-NH_2	−1.35	0.00	0.00	0.00	6.53	6.57 (−0.04)
II-40	*o*-CN	−0.30	0.00	0.00	0.00	7.44	7.06 (0.38)
II-41	*o*-OPr	0.92	1.00	0.00	0.00	7.57	7.79 (−0.22)
II-42	*o*-OBu	1.38	1.00	0.00	0.00	7.37	7.49 (−0.12)
II-43	*o*-OCH_2Ph	1.48	1.00	0.00	0.00	6.90	7.41 (−0.51)
II-44	*o*-OH	−0.80	0.00	0.00	0.00	7.55	6.90 (0.65)
II-45	*m*-Me	0.54	0.00	0.00	1.04	6.30	6.44 (−0.14)
II-46	*m*-*tert*-Bu	1.85	0.00	0.00	2.17	5.37	4.95 (0.42)
II-47	*m*-OMe	0.03	0.00	0.00	2.07	6.34	5.96 (0.38)
II-48	*m*-F	0.26	0.00	0.00	0.35	7.35	6.87 (0.48)
II-49	*m*-Cl	0.79	0.00	0.00	0.80	6.63	6.47 (0.16)
II-50	*m*-NO_2	−0.03	0.00	0.00	1.44	6.30	6.30 (0.00)
II-51	*m*-NH_2	−1.14	0.00	0.00	0.97	5.94	6.19 (−0.25)
II-52	*m*-CN	−0.32	0.00	0.00	0.60	6.11	6.73 (−0.62)
II-53	*m*-CF_3	0.98	0.00	0.00	1.61	5.48	5.94 (−0.46)
II-54	*p*-Me	0.52	0.00	0.81	0.00	6.31	6.47 (−0.16)
II-55	*p*-*n*-Pr	1.43	0.00	2.86	0.00	5.23	4.62 (0.61)
II-56	*p*-*tert*-Bu	1.82	0.00	2.05	0.00	5.24	4.80 (0.44)
II-57	*p*-OMe	−0.08	0.00	1.92	0.00	5.86	5.81 (0.05)
II-58	*p*-F	0.21	0.00	0.59	0.00	6.36	6.68 (−0.32)
II-59	*p*-Cl	0.77	0.00	1.46	0.00	5.84	5.95 (−0.11)
II-60	*p*-NO_2	0.03	0.00	1.38	0.00	5.42	6.17 (−0.75)
II-61	*p*-NH_2	−1.35	0.00	0.72	0.00	6.26	6.10 (0.16)
II-62	*p*-CN	−0.30	0.00	2.17	0.00	5.64	5.62 (0.02)
II-63	2,3-$(OMe)_2$	−0.05[e]	0.00	0.00	2.07	5.71	5.96 (−0.25)
II-64	2,4-$(OMe)_2$	−0.16[e]	1.00	1.92	0.00	6.04	6.75 (−0.71)
II-65	2,5-$(OMe)_2$	−0.05[e]	1.00	0.00	2.07	6.81	6.91 (−0.10)
II-66[f]	2,6-$(OMe)_2$	−0.16[e]	0.00	0.00	0.00	6.09	7.07
II-67	2-OMe,5-Me	0.46[e]	1.00	0.00	1.04	7.34	7.41 (−0.07)
II-68	2-OMe,5-F	0.18[e]	1.00	0.00	0.35	8.69	7.83 (0.86)

a) π value for monosubstituted anisoles. *b*) Indicator variable which takes the value of one for *o*-alkoxy groups and zero for others. *c*) Taken from a brochure distributed by Dr. A. Verloop. *d*) Δ, the difference between observed and calculated values. *e*) Value summed up for component substituents. *f*) Omitted from the calculation.

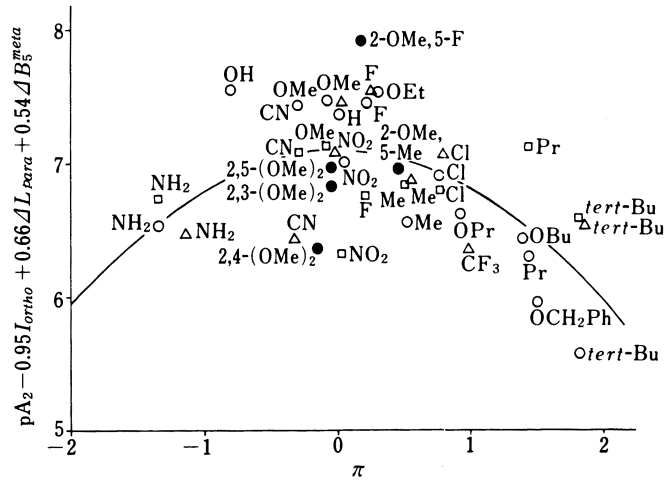


Fig. 4. Plots of $pA_2 - 0.95I_{ortho} + 0.66\Delta L_{para} + 0.54\Delta B_5^{meta}$ *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative; ●, disubstituted derivative.

TABLE VIII. Correlation Coefficient Matrix (r) for the Parameters of Eq. 7

	π^2	I_{ortho}	ΔL_{para}	ΔB_5^{meta}
π^2	1.00			
I_{ortho}	0.10	1.00		
ΔL_{para}	0.10	0.15	1.00	
ΔB_5^{meta}	0.05	0.04	0.33	1.00

operative on the conformation of the 2-OMe group. The hydrogen-bond formation, being a short-range stereosensitive interaction, may be highly dependent on the stereochemistry of the hydrogen acceptor substituents. The fact that the *o*-NO_2 and *o*-CN compounds did not require the I_{ortho} parameter may be in accord with this property of hydrogen-bonding. The locations of the hydrogen accepting site for the *o*-NO_2 and *o*-CN groups differ from that in the case of the alkoxy substituents.

In Table VIII, the intercorrelation between independent variables for thirty-eight derivatives was shown to be almost insignificant. Equation 7 shows that substituents with a π value close to zero are favorable for the activity. It also indicates that an alkoxy substituent at the *o*-position and small substituents at the *m*- and *p*-positions are needed for high activity. The most favorable substituent is *o*-OMe. The smallest *m*-substituent F could also be favorable, as was experimentally observed in the 2-OMe-5-F derivative (II-68).

The Analysis for the Whole Series of Analogs

Finally, analysis of the combined series of analogs was performed to give Eq. 8, with the parameters used in Eqs. 2 and 7 for individual series. The calculated pA_2 value of each compound is listed in Table IX.

$$pA_2 = -0.22\Sigma\pi^2 - 0.17\Sigma\pi + 0.35I(\mathrm{A}) + 0.99I_{ortho}(\mathrm{B}) - 0.53\Delta B_5^{meta}(\mathrm{B}) - 0.65\Delta L_{para}(\mathrm{B}) + 6.70$$
$$(0.12)\quad (0.13)\quad (0.31)\quad (0.29)\quad (0.18)\quad (0.16)\quad (0.34)$$
$$(n=59,\ r=0.92,\ s=0.37,\ F=48.25) \qquad (8)$$

In Eq. 8, A and B in parentheses mean that the parameter applies to the corresponding

TABLE IX. Calculated pA_2 values from Eq. 8

Compd. No.	Obsd.	Calcd. (Δ)[a]	Compd. No.	Obsd.	Calcd. (Δ)[a]
II-1	7.75	7.71 (0.04)	II-39	6.53	6.86 (−0.33)
II-2	7.54	7.56 (−0.02)	II-40	7.44	7.08 (0.36)
II-3	7.65	7.71 (−0.06)	II-41	7.57	7.74 (−0.17)
II-4	7.42	7.68 (−0.26)	II-42	7.37	7.44 (−0.07)
II-5	7.11	7.50 (−0.39)	II-43	6.90	7.36 (−0.46)
II-6	7.24	7.43 (−0.19)	II-44	7.55	7.04 (0.51)
II-7	7.47	7.56 (−0.09)	II-45	6.30	6.37 (−0.07)
II-8	7.87	7.71 (0.16)	II-46	5.37	4.90 (0.47)
II-9	7.90	7.68 (0.22)	II-47	6.34	5.96 (0.38)
II-10	7.66	7.50 (0.16)	II-48	7.35	6.82 (0.53)
II-11	7.60	7.61 (−0.01)	II-49	6.63	6.39 (0.24)
II-12	7.32	7.56 (−0.24)	II-50	6.30	6.30 (0.00)
II-13	6.87	6.99 (−0.12)	II-51	5.94	6.43 (−0.49)
II-14	8.02	7.71 (0.31)	II-52	6.11	6.77 (−0.66)
II-15	7.57	7.68 (−0.11)	II-53	5.48	5.86 (−0.38)
II-16	7.35	7.50 (−0.15)	II-54	6.31	6.40 (−0.09)
II-17	7.28	7.43 (−0.15)	II-55	5.23	4.56 (0.67)
II-18	8.04	7.73 (0.31)	II-56	5.24	4.75 (0.49)
II-19	7.85	7.55 (0.30)	II-57	5.86	5.83 (0.03)
II-20	7.68	7.64 (0.04)	II-58	6.36	6.64 (−0.28)
II-21	7.88	7.61 (0.27)	II-59	5.84	5.87 (−0.03)
I′	8.42	8.06 (0.36)	II-60	5.42	6.16 (−0.74)
II-31	7.37	7.06 (0.31)	II-61	6.26	6.40 (−0.14)
II-32	6.57	6.92 (−0.35)	II-62	5.64	5.68 (−0.04)
II-33	6.30	6.41 (−0.11)	II-63	5.71	5.97 (−0.26)
II-34	5.57	6.08 (−0.51)	II-64	6.04	6.83 (−0.79)
II-35	8.48	7.99 (0.49)	II-65	6.81	6.97 (−0.16)
II-36	7.45	7.02 (0.43)	II-67	7.34	7.39 (−0.05)
II-37	6.91	6.82 (0.09)	II-68	8.69	7.84 (0.85)
II-38	7.01	7.05 (−0.04)			

a) Δ, the difference between observed and calculated values.

rings. An indicator variable I(A) which takes the value of one for the derivatives with R_2 = 3,4,5-$(OMe)_3$ was newly introduced, since the upward deviation in the activity of the 3,4,5-$(OMe)_3$ derivative (I′) was not accounted for by Eq. 2. As the hydrophobic parameter, $\Sigma\pi$ was used since the coefficient of the π^2 term in Eq. 2 is close to that in Eq. 7. Equation 8 shows that actually a single optimum value, $\Sigma\pi = -0.39$, exists for the total hydrophobicity of the entire molecule, which presumably reflects the requirements of the transport process. Compounds having various R_3 substituents (II-23—30) were not included in Eq. 8, since relevant physicochemical parameters were not found. The pattern of the activity variations, suggesting an optimum hydrophobicity, in these compound series, however, seems to conform with Eq. 8 as described above.

In summary, the above quantitative analyses of the effects of substituents on the A and B rings are considered to have revealed the most effective structural conditions for α-blocking activity.

Experimental

α-Blocking Activity——Pharmacological procedures using rabbit thoracic aorta were described previously.[3]

Hydrophobic Parameter——As the hydrophobic parameter for substituents R_2, the π value[8] estimated from the

monosubstituted benzene system was adopted. For substituents R_4, the π value for substituted anisoles estimated according to the following equation[12] was used, as described previously.[5]

$$\pi(\text{X/subst. anisoles}) = 0.924\pi_X + 0.272\sigma_X^0 - 0.193\rho_X(para) + 0.037$$

In this equation, π_X is the π value of the substituents X in monosubstituted benzenes, σ_X^0 is a "σ" value representing the electron-withdrawing effect of substituents X applicable to cases in which the reaction center is insulated from direct conjugation with X.[13] ρ_X is the susceptibility constant of substituent X to the electronic effect of the OMe group on the partitioning in the 1-octanol/water system.[12]

Compounds

Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a JASCO A-202 or Hitachi 270-30 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (High MS) were measured using a JEOL DX-300 mass spectrometer.

Preparation of α-[(Phenoxyethylamino)propyl]-α-phenylacetonitriles (II) : (Method A): α-Isopropyl-α-[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-α-phenylacetonitrile (II-1)——A solution of α-(2-formylethyl)-α-isopropyl-α-phenylacetonitrile (III-1, 3.00 g) and 2-(2-methoxyphenoxy)ethylamine (2.00 g) in EtOH (70 ml) was refluxed for 1.5 h, then cooled with ice water, and $NaBH_4$ (0.53 g) was added. The mixture was stirred at room temperature for 2.5 h, and then concentrated. The residue was acidified with aqueous HCl and washed with Et_2O. The aqueous layer and the insoluble oily layer were combined, made alkaline with K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (95 : 5) as eluents to give II-1 (3.80 g, 87%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.78 and 1.20 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 1.72 (1H, s, NH), 2.91 (2H, t, J=5.5 Hz, $NC\underline{H}_2CH_2O$), 3.83 (3H, s, OCH_3), 4.07 (2H, t, J=5.5 Hz, $NCH_2C\underline{H}_2O$), 6.89 (4H, s, aromatic protons). High MS m/z: 366.2318 (M^+) (Calcd for $C_{23}H_{30}N_2O_2$ 366.2307).

Compounds II-2—10, 12—17, 22—38, 40—43, 45—50, 52—60, 62—68 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Tables I—III.

(Method B): 3-[1-(Cyano-1-isopropyl-4-[[2-(2-methoxyphenoxy)ethyl]amino]butyl]-*N*,*N*-dimethylbenzamide (II-11)——A mixture of 3-(4-chloro-1-cyano-1-isopropylbutyl)-*N*,*N*-dimethylbenzamide (IV-1, 0.64 g) and 2-(2-methoxyphenoxy)ethylamine (0.70 g) was stirred at 95 °C for 10 h. After cooling, the mixture was acidified with aqueous HCl and washed with Et_2O. The aqueous layer was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed with aqueous K_2CO_3. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (95 : 5) as eluents to give II-11 (0.47 g, 51%) as a yellowish brown oil. IR ν_{max}^{liq} cm^{-1}: 2236 (CN), 1638 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.78, 1.20 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.18 (1H, s, NH), 2.64 (2H, t, J=6.5 Hz, $CH_2CH_2C\underline{H}_2N$), 2.92 (2H, t, J=5.0 Hz, $NC\underline{H}_2CH_2O$), 2.95, 3.07 (each 3H, br s, $CON(CH_3)_2$), 3.83 (3H, s, OCH_3), 4.07 (2H, t, J=5.0 Hz, $NCH_2C\underline{H}_2O$), 6.89 (4H, s, aromatic protons), 7.42 (4H, s, aromatic protons). High MS m/z: 437.2690 (M^+) (Calcd for $C_{26}H_{35}N_3O_3$ 437.2678).

Compounds II-18, 20 and 21 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Table I.

α-(4-Aminophenyl)-α-isopropyl-α-[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]acetonitrile (II-19)——A solution of α-isopropyl-α-[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-α-(4-nitrophenyl)acetonitrile (II-18, 2.20 g) in MeOH (20 ml) was hydrogenated over PtO_2 (22 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (98 : 2) as eluents to give II-19 (1.90 g, 93%) as a pale yellow oil. The obtained free base was converted into the oxalate in a usual manner and the resulting salt was recrystallized from H_2O–EtOH to give pale yellow crystals, mp 155—158 °C. IR ν_{max}^{KBr} cm^{-1}: 2235 (CN). ^{1}H-NMR (DMSO-d_6) δ: 0.72, 1.07 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.23 (2H, t, J=5.5 Hz, $NC\underline{H}_2CH_2O$), 3.77 (3H, s, OCH_3), 4.18 (2H, t, J=5.5 Hz, $NCH_2C\underline{H}_2O$). *Anal.* Calcd for $C_{23}H_{31}N_3O_2 \cdot 2C_2H_2O_4$: C, 57.75; H, 6.28; N, 7.48. Found: C, 57.68; H, 6.35; N, 7.41.

Compounds II-39, 51 and 61 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Tables I and III.

α-[3-[[2-(2-Hydroxyphenoxy)ethyl]amino]propyl]-α-isopropyl-α-(3,4,5-trimethoxyphenyl)acetonitrile (II-44)——A solution of α-[3-[[2-(2-benzyloxyphenoxy)ethyl]amino]propyl]-α-isopropyl-α-(3,4,5-trimethoxyphenyl)acetonitrile (II-43, 0.50 g) in MeOH (20 ml) was hydrogenated over PtO_2 (50 mg) under atmospheric pressure at room temperature. After usual operations including purification by silica gel chromatography, II-44 (0.25 g, 60%) was obtained as the free base (a colorless oil). It was converted into the fumarate in a usual manner and the resulting salt was recrystallized from MeOH to give colorless plates, mp 190.5—192.5 °C. IR ν_{max}^{KBr} cm^{-1}: 2250 (CN). ^{1}H-NMR (CD_3OD) δ: 0.79 and 1.22 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.75 (3H, s, OCH_3), 3.85 (6H, s, 2 × OCH_3), 4.21 (2H, t, J=5.0 Hz, $NCH_2C\underline{H}_2O$), 6.68 (2H, s, olefinic protons), 6.72 (2H, s, aromatic protons). *Anal.* Calcd for $C_{25}H_{34}N_2O_5 \cdot C_4H_4O_4$: C, 62.35; H, 6.86; N, 5.01. Found: C, 62.18; H, 6.70; N, 4.95.

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